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Four new tetraazacrown ethers containing two 8-hydroxyquinoline side arms were prepared first by reductive amination of 8-acetoxyquinolin-2-carbaldehyde with the appropriate tetraazacrown ether containing two microring NH functions (see our Technical Report No. 4). The resulting bis(8-acetoxy-1-quinolinylmethyl)-substituted tetraazacrown ethers were treated with 10% aqueous KOH followed by acid to form the *N,N'*-bis(8-hydroxy-2-quinolinylmethyl-substituted tetraazacrown ethers.

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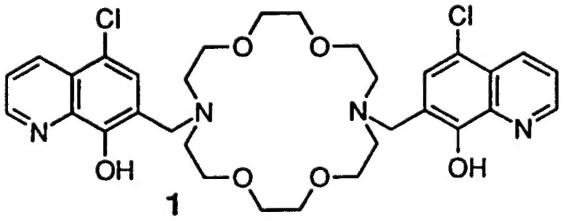
Introduction

A number of crown ether-containing FIPs have been prepared with various fluorophore sidearms including anthracene, coumarin, merocyanine, and benzoxazinone groups.[1-6] Crown ethers containing oximic and Schiff-base sidearms have also been prepared.[2] Improvements in metal ion complexing ability and selectivity have been observed when proton-ionizable chromophoric or fluorophoric units are attached to the crown ring as side arms.[3] New 5-chloro-8-hydroxyquinoline (CHQ)-substituted azacrown ethers where CHQ was attached through its 7-position (**1**) or its 2-position (**2**) have been synthesized in our laboratory.[5,6] The ion selectivities demonstrated by **1** and **2** were much greater than those of the parent diaza-18-crown-6 macrocycle.[6] Particularly striking is the selectivity of compound **1** for Ni(II) over Cu(II) (log K = 11.4 and 10.1, respectively, in methanol) and its strong complexing ability with Mg^{2+} and Ca^{2+}. Indeed, ligand **1** is a very effective sensor for Mg^{2+} ions.[7] Compound **2**, with attachment of CHQ through its 2-position, displays strong complexation in methanol with K^+ and Ba^{2+} (log K = 6.61 and 12.2, respectively) but not with Mg^{2+} or Cu^{2+}. The crystal structure of the complex of Ba^{2+} with **2** shows that both 8-CHQ groups are bidentate chelators of Ba^{2+} and both are juxtaposed on the same side of the complex forming a cryptate-like structure.[6]



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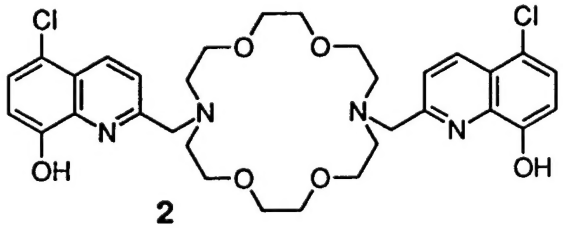

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This report describes the preparation of new 8-hydroxyquinoline-(8-HQ)-substituted tetraazacrown ethers designed to selectively bind transition and post-transition metal ions with a concomitant modulation in the absorption and fluorescence spectra of the compounds. Tetraazacrown ethers have been shown to selectively complex the target group of metal ions.[8]

Results and Discussion

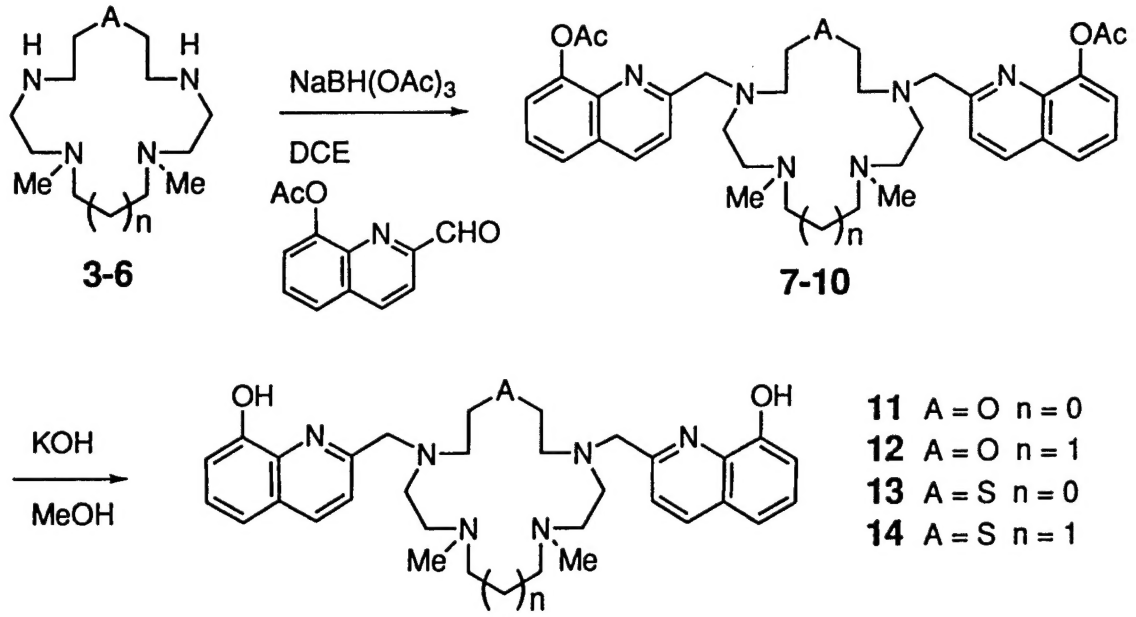
Synthesis of Quinoline Derivative-containing Tetraazacrown Ethers. We have

reported two methods of attaching 5-chloro-8-hydroxyquinoline to diaza-18-crown-6 (to form **1** and **2**).[5] Ligand **2** was prepared by a nucleophilic substitution of the secondary nitrogens on the macrocycle ring on halomethyl-substituted 8-methoxyquinoline followed by removal of the methyl groups.[5] Ligand **1** was prepared by conversion of the secondary amines of the macrocycle to (methoxymethyl)amines which are active electrophilic reagents in the Mannich reaction and react readily with the electron rich phenolic side of 5-chloro-8-hydroxyquinoline.[5] We have previously reported the synthesis of 4 new tetraaza-15-(and-16)-crown-5 ligands containing two unsubstituted ring N-H functions.[9] We attempted to prepare the quinoline derivative-containing tetraaza macrocycles by the above mentioned two methods. Unfortunately, no desired products were obtained.

Reactions of aldehydes with primary or secondary amines in the presence of reducing agents to give secondary or tertiary amines, respectively, known as reductive amination, are useful methods to alkylate amine groups. Direct reductive amination of aldehydes with amines using sodium triacetoxyborohydride ($NaBH(OAc)_3$) as a reducing agent has been developed for a wide variety of substrates.[10] Compared to other hydride reducing agents such as sodium cyanoborohydride ($NaBH_3CN$), $NaBH(OAc)_3$ is mild, less toxic and exhibits remarkable selectivity as a reducing agent.[10]

Reductive amination of 8-hydroxyquinolin-2-carboxaldehyde with a tetraazacrown ether did not occur, possibly because of the presence of the phenolic OH group. However, when tetraaza macrocycles **3-6** were treated with 8-acetoxyquinolin-2-carboxaldehyde in the presence of $NaBH(OAc)_3$, 8-acetoxyquinoline-substituted macrocycles **7-10** were formed in good yields (Scheme 1). Products **7-10** could not be purified by chromatography because they were hydrolyzed by the solvent system used, and, thus, were treated without purification with KOH to form 8-HQ-containing ligands **11-14** in 71%-78% yields. When working up macrocycles **11-14** following hydrolysis of the acetates, the solution was adjusted to pH ~ 10. In this pH range, the tetraazacrown ethers contain one or more molecules of HCl as demonstrated by the elemental analyses for **11**, **12** and **14**.

Another approach to prepare 8-HQ-substituted **11** is shown in Scheme 2. The 8-HQ pendant arms were attached to the aliphatic nitrogen by stepwise reductive amination before



Scheme 1. Syntheses of 8-hydroxyquinoline-substituted tetraazacrown ethers *via* reductive amination

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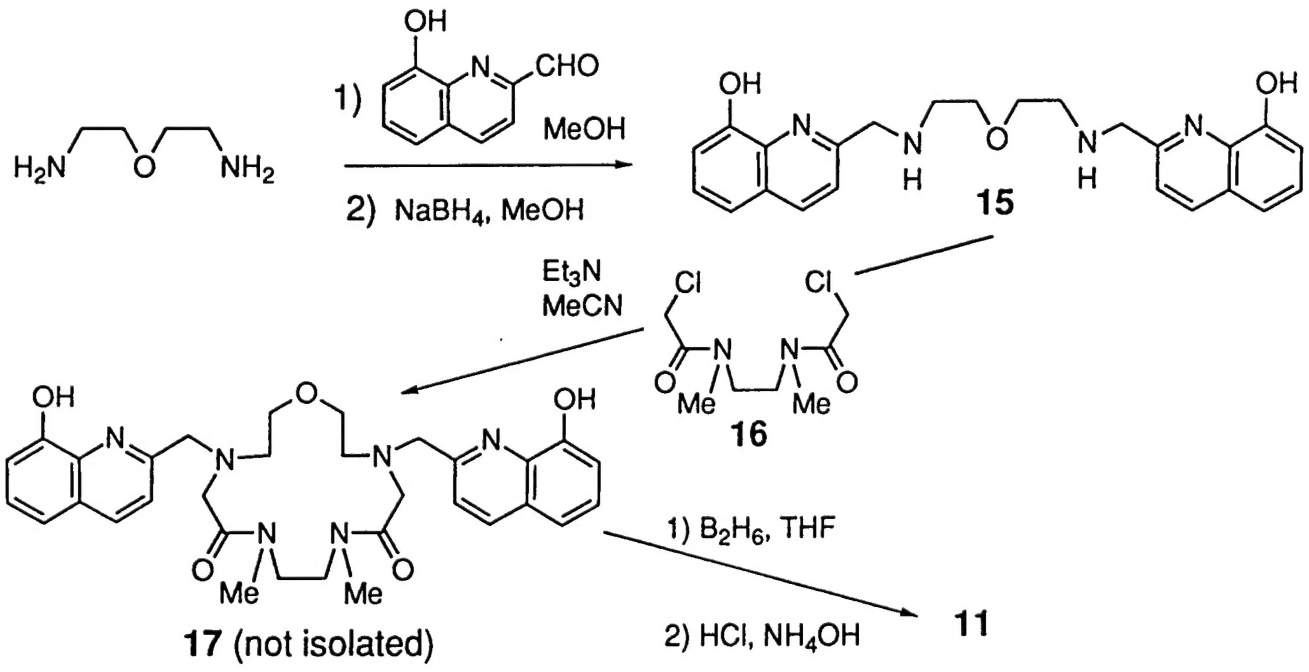

Scheme 2. Alternate synthesis of **11**

cyclization to form **15**. Compound **15** was cyclized with crab-like bis(α-chloroamide) **16** to give the intermediate macrocyclic diamide **17**. To avoid deprotonation of the phenolic OH group, triethylamine was used instead of Na_2CO_3 in the cyclization reaction. The resulting bisamide was reduced by the borane-THF complex to give **11** in a 27% overall yield. Aqueous HCl needed to be added to the reaction mixture to destroy the complex with borane. Treatment of the diamide with $LiAlH_4$ gave a lower yield. Compared to the approach in Scheme 1, both the cyclization and reduction steps (Scheme 2) gave lower yields. Thus, the direct attachment of the quinolinecarbaldehyde to the secondary amines of the macrocycle ring is a more convenient way to prepare macrocycles with quinoline derivatives as side arms.

Experimental Section

The ^1H and ^{13}C NMR spectra were recorded at 200 or 300 MHz and 50 or 75 MHz in $CDCl_3$ unless otherwise noted. MS spectra were determined using chemical ionization (CI) and fast atom bombardment (FAB) methods. All starting materials were either purchased from commercial sources or synthesized by known methods: 8-acetoxyquinolin-2-carbaldehyde[11] and starting tetraaza-15(-16)-crown ethers **3-6**.[9]

General Procedure A: Reductive Amination of Quinolinecarboxaldehydes with Tetraazacrown Ethers (Scheme 1). A mixture of the quinolinecarboxaldehyde and the macrocyclic diamine in $ClCH_2CH_2Cl$ was stirred with 1.3-1.6 equiv of $NaBH(OAc)_3$ under a N_2 atmosphere at rt. The reaction was monitored by TLC. When the reaction was completed, 1*N* HCl was added to terminate the reaction. Then 1*N* NaOH was added to adjust the pH value of the solution to pH 10-12. The solution was then extracted several times by portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH) to give the product.

7,13-Bis((8-acetoxy-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (7) (Scheme 1). Compound **7** (210 mg, 82%) was obtained as an oil according to general procedure A from 8-acetoxyquinolin-2-carboxaldehyde (172 mg, 0.8 mmol) and **3** (98

mg, 0.4 mmol); ^{1}H NMR δ 8.06 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 8.1, 1.5 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.43 (dd, J = 7.4, 8.1 Hz, 2H), 7.35 (dd, J = 7.4, 1.5 Hz, 2H), 3.93 (s, 4H), 3.47 (t, J = 4.2 Hz, 4H), 2.89 (t, J = 6.3 Hz, 4H), 2.78-2.75 (m, 12H), 2.42 (s, 6H), 2.32 (s, 6H); ^{13}C NMR δ 169.8, 160.3, 147.4, 140.3, 136.3, 128.6, 125.8, 125.7, 122.2, 121.3, 70.1, 61.5, 55.0, 54.0, 53.9, 52.1, 43.5, 21.1; MS (FAB) *m/z* 665 (MNa^+); HRMS (FAB) Calcd for $C_{36}H_{47}N_6O_5$ (MH^+): 643.3608, found: 643.3582.

8,14-Bis((8-acetoxy-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecane (8) (Scheme 1). Compound **8** (279 mg, 85%) was obtained as an oil according to general procedure A from 8-acetoxyquinolin-2-carboxaldehyde (215 mg, 1 mmol) and **4** (129 mg, 0.5 mmol); ^{1}H NMR δ 8.09 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.66 (dd, J = 8.3, 1.5 Hz, 2H), 7.46 (dd, J = 7.6, 8.3 Hz, 2H), 7.38 (dd, J = 7.6, 1.5 Hz, 2H), 3.95 (s, 4H), 3.53 (t, J = 4.6 Hz, 4H), 2.89 (t, J = 6.4 Hz, 4H), 2.81 (t, J = 5.1 Hz, 4H), 2.64 (m, 8H), 2.46 (s, 6H), 2.29 (s, 6H), 1.76 (p, J = 6.6 Hz, 2H); ^{13}C NMR δ 169.9, 160.9, 147.4, 140.3, 136.3, 128.7. 125.8, 125.8, 122.1, 121.3, 70.0, 61.5, 55.4, 55.0, 54.1, 52.0, 42.8, 21.1; MS (FAB) *m/z* 657 (MH^+), 679 (MNa^+); HRMS (FAB) Calcd for $C_{37}H_{49}N_6O_5$ (MH^+): 657.3764, found: 657.3745.

7,13-Bis((8-acetoxy-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-thiacyclopentadecane (9) (Scheme 1). Compound **9** (336 mg, 88%) was obtained as an oil according to general procedure A from 8-acetoxyquinolin-2-carboxaldehyde (250 mg, 1.2 mmol) and **5** (150 mg, 0.6 mmol); ^{1}H NMR δ 8.10 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.67 (dd, J = 8.1, 1.5 Hz, 2H), 7.46 (dd, J = 7.5, 8.1 Hz, 2H), 7.40 (dd, J = 7.5, 1.5 Hz, 2H), 3.95 (s, 4H), 2.92-2.87 (m, 4H), 2.77-2.70 (m, 8H), 2.63-2.58 (m, 8H), 2.48 (s, 6H), 2.21 (s, 6H); ^{13}C NMR δ 169.9, 160.7, 147.4, 140.4, 136.3, 128.7, 125.8, 125.7, 122.0, 121.3, 61.8, 55.9, 55.7, 54.9, 51.9, 43.5, 29,6, 21.1; MS (FAB) *m/z* 681 (MNa^+); HRMS (FAB) Calcd for $C_{36}H_{47}N_6O_4S$ (MH^+): 659.3379, found: 659.3382.

8,14-Bis((8-acetoxy-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-thiacyclopentadecane (10) (Scheme 1). Compound **10** (269 mg, 80%) was obtained as an oil according to general procedure A from 8-acetoxyquinolin-2-carboxaldehyde (215 mg, 1 mmol) and **6** (137 mg, 0.5 mmol); ^{1}H NMR δ 8.10 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.67 (dd, J = 8.1, 1.5 Hz, 2H), 7.47 (dd, J = 7.5, 8.1 Hz, 2H), 7.39 (dd, J = 7.5, 1.5 Hz, 2H), 3.95 (s,

4H), 2.90-2.85 (m, 4H), 2.74-2.71 (m, 8H), 2.57-2.46 (m, 14H), 2.18 (s, 6H), 1.68 (p, J = 6.6 Hz, 2H); ^{13}C NMR δ 169.9, 160.9, 147.4, 140.4, 136.3, 128.7, 125.7, 121.9, 121.3, 61.7, 55.6, 55.4, 54.8, 52.0, 43.3, 29.9, 25.3, 21.1; MS (FAB) *m/z* 673 (MH^+), 695 (MNa^+); HRMS (FAB) Calcd for $C_{37}H_{49}N_6O_4S$ (MH^+): 673.3536, found: 673.3542.

General Procedure B: Removal of Acetate Groups on Macrocyclic Compounds 7-10. A solution of the 8-acetoxy-2-quinolinylmethyl-substituted macrocyclic compound in MeOH was cooled to 0 °C and stirred vigorously while 10% aqueous KOH was slowly added. The mixture was stirred at rt for 30 min and neutralized with 3 *N* HCl to pH 8. The solution was then extracted several times by portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and evaporated to give the crude product. The crude product was purified by flash chromatography on silical gel (70-100:5:1/CH_2Cl_2:MeOH: NH_4OH) to give the product.

7,13-Bis((8-hydroxy-2-quinolinyl)methyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (11) (Scheme 1). Compound **11** (154 mg, 92%) was obtained as an oil according to general procedure B from **7** (193 mg, 0.3 mmol); ^{1}H NMR (CD_3OD) δ 8.20 (d, J = 12.0 Hz, 2H), 7.41-7.35 (m, 6H), 7.24-7.19 (m, 2H), 4.08 (s, 4H), 3.73 (s, 4H), 3.91 (t, J = 8.6 Hz, 4H), 3.08 (t, J = 8.6 Hz, 4H), 2.88 (s, 6H), 2.67 (s, 8H); ^{13}C NMR (CD_3OD) δ 159.3, 153.2, 139.4, 139.2, 130.5, 128.5, 122.2, 120.3, 113.8, 68.0, 59.4, 58.3, 56.8, 52.6, 51.0, 42.9; MS (FAB) *m/z* 582 (MNa^+), 604 ($M+Na^+-H^+$), 626 ($M+2Na^+-2H^+$); HRMS (FAB) Calcd for $C_{32}H_{43}N_6O_3$ (MH^+): 559.3396, found: 559.3377. Anal. Calcd for $C_{32}H_{42}N_6O_3 \cdot 6HCl \cdot 2.5H_2O$: C, 46.73; H, 6.49. Found: C, 46.82; H, 6.45.

8,14-Bis((8-hydroxy-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-oxacyclohexadecane (12) (Scheme 1). Compound **12** (376 mg, 94%) was obtained as an oil according to general procedure B from **8** (460 mg, 0.7 mmol); ^{1}H NMR δ 8.06 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 8.5 Hz, 2H), 7.36 (dd, J = 7.8, 7.3 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 7.3 Hz, 2H), 3.92 (s, 4H), 3.55 (t, J = 5.1 Hz, 4H), 2.87-2.81 (m, 8H), 2.60 (t, J = 6.9 Hz, 4H), 2.49 (t, J = 6.9 Hz, 4H), 2.20 (s, 6H), 1.65 (p, J = 6.9 Hz, 2H); ^{13}C NMR δ 158.7, 152.4, 137.7, 136.4, 127.7, 127.2, 122.1, 117.6, 110.2, 69.9, 61.7, 55.9, 55.3, 54.4, 53.0, 43.5, 25.0; MS (FAB) *m/z* 595 (MNa^+), 617 ($M+Na^+-H^+$) 639 ($M+2Na^+-2H^+$); HRMS (FAB) Calcd for $C_{33}H_{45}N_6O_3$ (MH^+): 573.3553, found: 573.3568. Anal. Calcd for $C_{33}H_{44}N_6O \cdot 6HCl \cdot 2.5H_2O$: C,

47.38; H, 6.63. Found: C, 47.12; H, 6.55.

7,13-Bis(8-hydroxyquinolin-2-ylmethyl)-1,4-dimethyl-1,4,7,13-tetraaza-10-thia-cyclopentadecane (13) (Scheme 1). Compound **13** (258 mg, 90%) was obtained as an oil according to general procedure B from **9** (320 mg, 0.5 mmol); ^{1}H NMR δ 8.08 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.41 (dd, J = 7.6, 8.1 Hz, 2H), 7.29 (dd, J = 1.2, 8.3 Hz, 2H), 7.15 (dd, J = 1.2, 7.6 Hz, 2H), 3.93 (s, 4H), 2.91-2.86 (m, 4H), 2.75-2.70 (m, 8H), 2.60-2.55 (m, 8H), 2.18 (s, 6H); ^{13}C NMR δ 158.4, 152.4, 137.6, 136.5, 127.7, 127.4, 122.0, 117.7, 110.3, 61.8, 56.1, 55.9, 55.2, 52.5, 43.3, 29.5; MS (FAB) *m/z* 597 (MNa^+), 619 ($M+2Na^+-H^+$), 641 ($M+3Na^+-H^+$); HRMS (FAB) Calcd for $C_{32}H_{43}N_6O_2S$ (MH^+): 575.3168, found: 575.3151.

8,14-Bis((8-hydroxy-2-quinolinyl)methyl)-1,5-dimethyl-1,5,8,14-tetraaza-11-thia-cyclohexadecane (14) (Scheme 1). Compound **14** (327 mg, 89%) was obtained as an oil according to general procedure B from **10** (420 mg, 0.6 mmol); ^{1}H NMR δ 8.08 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.15 (d, J = 7.5 Hz, 2H), 3.94 (s, 4H), 2.87-2.84 (m, 4H), 2.74-2.67 (m, 8H), 2.54 (t, J = 6.6 Hz, 4H), 2.47 (t, J = 6.9 Hz, 4H), 2.17 (s, 6H), 1.68 (p, J = 6.9 Hz, 2H); ^{13}C NMR δ 158.5, 152.3, 137.6, 136.5, 127.7, 127.3, 122.1, 117.8, 110.2, 61.6, 55.7, 55.4, 54.9, 52.3, 43.4, 29.8, 25.4; MS (FAB) *m/z* 589 (MH^+), 611 ($M+Na^+-H^+$), 633 ($M+2Na^+-2H^+$); HRMS (FAB) Calcd for $C_{33}H_{45}N_6O_2S$ (MH^+): 589.3324, found: 589.3340; Anal. Calcd for $C_{33}H_{44}N_6O_2S\cdot 2HCl\cdot H_2O$: C, 58.31; H, 7.12, N, 12.36. Found: C, 58.39; H, 7.08, N, 12.53.

N,N'-Bis((8-hydroxy-2-quinolinyl)methyl)-3-oxa-1,5-pentanediamine (15) (Scheme 2). To a solution of 8-hydroxyquinolin-2-carbaldehyde (173 mg, 1 mmol) in MeOH (10 mL) was added a solution of oxybis(ethyldiamine) (52 mg, 0.5 mmol) in MeOH. The reaction mixture was warmed in a water bath for 1 h. The solution was then concentrated to 5 mL and cooled in an ice bath. A solution of $NaBH_4$ in MeOH was added to the reaction mixture at rt. The reaction mixture was stirred for 1 h, filtered, and MeOH was removed under reduced pressure. The yellow powder obtained was dissolved in 30% aqueous HOAc and neutralized with aqueous Na_2CO_3. The solution was extracted with CH_2Cl_2, dried (Na_2SO_4) and evaporated to give the crude product. The crude product was purified by flash chromatography to give the product (167 mg, 80%) as a yellow oil; ^{1}H NMR δ 7.93 (d, J = 8.5 Hz, 2H), 7.34 (dd, J = 8.0, 7.8

Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.20 (dd, J = 8.0, 1.2 Hz, 2H), 7.10 (dd, J = 7.8, 1.2 Hz, 2H), 6.10 (br s, 4H), 4.11, (s, 4H), 3.67 (t, J = 5.0 Hz, 4H), 2.93 (t, J = 5.0 Hz, 4H); ^{13}C NMR δ 157.6, 152.7, 137.8, 136.4, 127.6, 127.2, 121.0, 117.6, 110.7, 70.2, 54.6, 48.6; MS (FAB) *m/z* 419 (MH^+); HRMS (FAB) Calcd for $C_{24}H_{27}N_4O_3$ (MH^+): 419.2083, found: 419.2077.

7-13-Bis((8-hydroxy-2-quinolinyl)methyl-1,4-dimethyl-1,4,7,13-tetraaza-10-oxacyclopentadecane (11) (Scheme 2). Compound **17** was prepared from 0.65 (1.55 mmol) of **15**, 0.37 g (1.55 mmol) of **16** (prepared from *N,N'*-dimethylethylenediamine), 1.25 g Et_3N (instead of Na_2CO_3) and 50 mL of MeCN as reported.[9] Macrocyclic diamide **17** was not purified. Crude **17** was reduced according with $LiAlH_4$ to give 230 mg (27% overall) of **11** which exhibited the same physical and spectral properties as **11** prepared above (Scheme 1).

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